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Prostate Cancer

Is Prostate-specific Membrane Antigen Positron Emission Tomography/Computed Tomography Imaging Cost-effective in Prostate Cancer: An Analysis Informed by the proPSMA Trial

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Abstract

Background: Before integrating prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) into routine care, it is important to assess if the benefits justify the differences in resource use.
Objective: To determine the cost-effectiveness of PSMA-PET/CT when compared with conventional imaging.
Design, setting, and participants: A cost-effectiveness analysis was developed using data from the proPSMA study. proPSMA included patients with high-risk prostate cancer assigned to conventional imaging or ^{68}Ga-PSMA-11 PET/CT with planned health economics data collected. The cost-effectiveness analysis was conducted from an Australian societal perspective.
Intervention: ^{68}Ga-PSMA-11 PET/CT compared with conventional imaging (CT and bone scan).
Outcome measurements and statistical analysis: The primary outcome from proPSMA was diagnostic accuracy (nodal and distant metastases). This informed a decision tree analysis of the cost per accurate diagnosis.
Results and limitations: The estimated cost per scan for PSMA PET/CT was AUD$1203, which was less than the conventional imaging cost at AUD$1412. PSMA PET/CT was thus dominant, having both better accuracy and a lower cost. This resulted in a cost of AUD $959 saved per additional accurate detection of nodal disease, and AUD$1412 saved for additional accurate detection of distant metastases. The results were most sensitive to variations in the number of men scanned for each ^{68}Ga-PSMA-11 production run. Subsequent research is required to assess the long-term costs and benefits of PSMA PET/CT-directed care.

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Conclusions: PSMA PET/CT has lower direct comparative costs and greater accuracy compared to conventional imaging for initial staging of men with high-risk prostate cancer. This provides a compelling case for adopting PSMA PET/CT into clinical practice.
Patient summary: The proPSMA study demonstrated that prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) better detects disease that has spread beyond the prostate compared with conventional imaging. Our analysis shows that PSMA PET/CT is also less costly than conventional imaging for the detection of disease spread.

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1. Introduction

Radiolabelled small molecules targeting prostate-specific membrane antigen (PSMA) with positron emission tomography (PET) allow whole-body imaging for detection of prostate cancer spread [1]. The proPSMA randomised controlled trial (RCT) recently provided high-level evidence of superior diagnostic accuracy of PSMA PET/computed tomography (CT) compared with conventional imaging (CI; CT of the abdomen/pelvis and bone scanning) for detection of metastatic disease [2]. It showed that ^{68}Ga-PSMA-11 PET/CT was more sensitive and specific at detecting pelvic lymph-node and distant metastatic disease in men with high-risk prostate cancer who are being considered for prostatectomy or radiotherapy.

Before integrating PSMA PET/CT into routine care, it is important to assess whether the additional benefits are justified by potential differences in the use of resources required for its implementation. This paper assesses the costs and outcomes (diagnostic accuracy) associated with the use of PSMA PET/CT compared with CI in staging men with high-risk prostate cancer using information collected as part of the proPSMA study.

2. Patients and methods

The design and conduct of the proPSMA study has been reported elsewhere [2]. In brief, proPSMA allocated high-risk prostate cancer patients being considered for prostatectomy or radiotherapy to first-line imaging with PSMA PET/CT or CI. The primary outcome was diagnostic accuracy using a predefined criterion encompassing histopathology, temporal changes in imaging, and biochemistry determined at the 6-month patient follow-up visit.

The population in the proPSMA study and subsequent economic analysis was high-risk prostate cancer patients, defined by PSA $\geq$ 20 ng/ml or International Society of Urological Pathology grade group 3–5 or clinical stage $\geq$ T3.

All sites participating in proPSMA were prospectively surveyed to provide information on ^{68}Ga-PSMA production, including whether purchased or manufactured in-house (Supplementary Table 1). For in-house manufacture, details were collected on specific consumables (including the gallium generator and cartridges or kit), equipment items (including the automated synthesis unit and high-performance liquid chromatography system), staff time for production and quality assurance (QA), and the dose (MBq) of radiopharmaceutical manufactured per production run.

A microcosting approach was applied using pricing information provided by one site to derive the cost for ^{68}Ga-PSMA production and the associated PET/CT scan, following the method of Segard et al [3] (Supplementary Table 2). The impact on the costs of variability in radiopharmaceutical generator prices, wages applied to time inputs, and the number of scans per ^{68}Ga-PSMA elution was tested in subsequent sensitivity analyses.

The costs and effects of using PSMA PET/CT compared with CI as observed in proPSMA were described using a decision tree (Fig. 1). Outcomes for the analysis were expressed in terms of accurate diagnoses (at 6 mo); this was the incremental difference in the probability-adjusted true positives minus the false negatives, with the probabilities and associated measures of accuracy derived from proPSMA (Table 1). The decision tree took into account the accuracy of the two imaging approaches with respect to pelvic lymph node (nodal) and distant metastases.

Costs were those associated with the production and delivery of both scanning modalities. Costs for PSMA PET/CT were as described above, while those for CI were informed by proscribed fees from the Australian Medicare Benefits Schedule [4] for CT and bone scans. Information on the time required for scan delivery was collected as part of proPSMA, capturing the length of time from administration of the radiopharmaceutical to the end of a scan. A societal perspective was adopted, including the costs to the patient associated with image delivery time, costed at the Australian average hourly wage for males as a proxy for the value of time [5].

3. Results

proPSMA showed that PSMA PET/CT was more accurate in detecting metastatic and nodal disease than CI (Table 1). In addition, delivery of PSMA PET/CT required an average of 1.5 h per patient, compared with 5.5 h for CI (not including the time interval between the acquisition of bone scans on separate days for CT).

Nine sites provided information on the production of ^{68}Ga-PSMA. Eight sites manufactured ^{68}Ga-PSMA in their on-site hospital radiopharmacy, with an average yield of 615 MBq of ^{68}Ga-PSMA per production run.

On the basis of an average dose per scan in proPSMA of 164 MBq, it was assumed in the base-case analysis that each ^{68}Ga-PSMA production run would provide a minimum of two scans (allowing for QA and potential wastage). The resulting cost per scan was AUD$1140 for PSMA PET/CT and AUD$1181 for CI. Adopting a societal perspective including delivery time, the cost per scan increased to AUD$1203 for PSMA PET/CT and AUD$1412 for CI.

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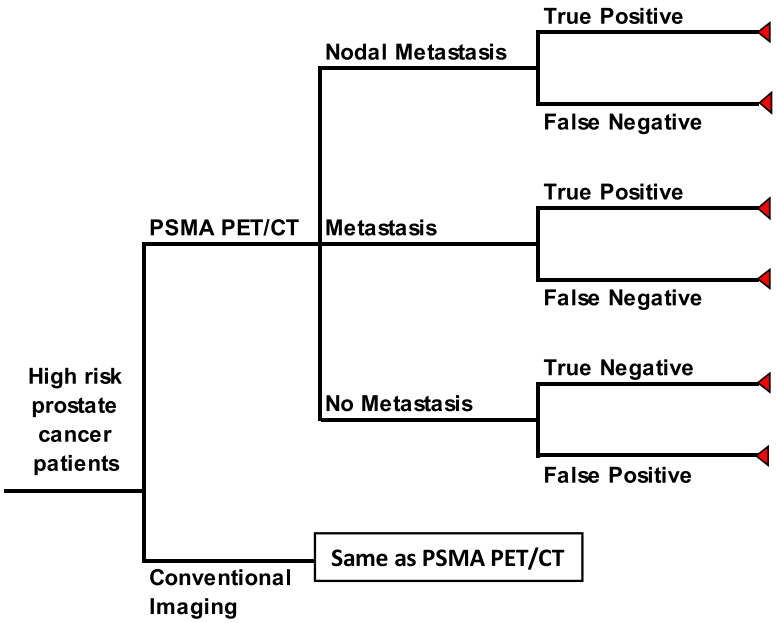

Fig. 1 – Decision tree l comparing prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) with conventional imaging.

Combining the cost per scan with the accuracy of detection, PSMA PET/CT would be dominant, as it is less costly and more accurate. Focusing on the accuracy of detection for each metastasis type separately, PSMA PET/CT was associated with AUD$959 saved per additional accurate detection of nodal disease compared with CI, and AUD$1412 saved per additional accurate detection of distant metastases. When weighted by the probability of metastasis detection as observed in proPSMA, and including the accuracy of detection for all possible metastatic states, the dominance of PSMA PET/CT resulted in a cost saving of AUD$428 per additional accurate diagnosis.

The weighted cost per metastasis detection was sensitive to the number of patients per elution and the cost components of both imaging techniques (Fig. 2). Assuming on one patient per ^{68}Ga-PSMA elution resulted in an incremental cost per additional case detected for Ga-PSMA compared with CI of AUD$2553 for nodal disease and AUD $3758 for metastatic disease, for a weighted cost per accurate diagnosis of AUD$1138. However, if three patient doses were obtained per elution, AUD$950 would be saved for an additional accurate diagnosis.

4. Discussion

This is the first economic evaluation to directly use data from a large RCT that demonstrated the superior accuracy of PSMA PET/CT in this setting. Our analysis indicates that PSMA PET/CT is dominant to CI in the short-term for staging men with high-risk disease, as it has greater diagnostic accuracy and is cheaper than CI.

Altering the detection of metastatic disease has implications for the downstream treatment of prostate cancer in terms of both health care service use and the impact on quality of life [6]. More accurate diagnosis of metastatic disease through the use of PSMA PET/CT is likely to result in more men receiving appropriate treatment for metastases, and thus not incurring the costs, lower survival, or poorer quality of life associated with an incorrect diagnosis. This is an important implication of this analysis that will require

Table 1 – proPSMA key results informing the economic evaluation.

	^{68}Ga–PSMA PET/CT (n = 145)	Conventional imaging (n = 150)
Distant metastases		
Sensitivity, % (95% confidence interval)	92 (81–100)	54 (34–74)
Specificity, % (95% confidence interval)	99 (98–100)	93 (88–97)
Nodal metastases		
Sensitivity, % (95% confidence interval)	83 (70–95)	23 (10–35)
Specificity, % (95% confidence interval)	99 (97–100)	96 (93–100)
Scan duration (h)	1.51	5.52[a]

CT = computed tomography; PET = positron emission tomography; PSMA = prostate–specific membrane antigen.
[a] The scan time for conventional imaging includes 47 min for acquisition of a bone scan with single–photon emission CT/CT and 15 min for acquisition of a CT scan.

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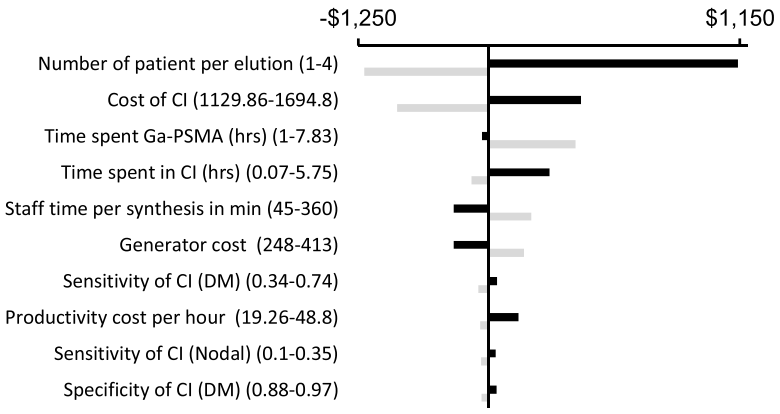

Fig. 2 – Tornado plot of deterministic sensitivity analysis. Black bars represent the variation in cost per additional accurate case detected using the minimum range. A variation towards the left-hand side of the graph favours PSMA positron emission tomography/computed tomography. CI = conventional imaging; DM = distant metastasis; PSMA = prostate-specific membrane antigen.

revisiting as the implementation of PSMA PET/CT scanning, and its implications for the management of men with prostate cancer, continues to be monitored.

There have been other analyses of the potential cost-effectiveness of PSMA PET/CT [7,8]. These studies were in different clinical settings, such as men who had castrate-resistant disease [8] or postretroperitoneal lymph node dissection [7]. Scholte et al [7] focused exclusively on men with existing nodal disease, while the balance of nodal and distant metastases in the population in the study by Gordon et al [8] was not reported. Our analysis shows superiority of PSMA PET/CT over CI in the detection of both nodal and distant metastases. Similarly, PSMA PET/CT accuracy in those papers was based on assumptions from the literature or small case series. A similar cohort-based analysis considered the cost implications of shifting between the use of ^{11}C-choline PET/CT or CI and PSMA PET/CT and found that if each additional PSMA PET/CT procedure added US $1466 or US$4312, respectively, the procedure would be considered cost-effective [9].

Our analysis differed in that key inputs were defined prospectively at the commencement of proPSMA [10], allowing us to reflect resource use within the study. Importantly, this included aspects of producing PSMA radiotracers that have been cited as being important contributors to cross-organisation and jurisdictional differences in the costs of providing such scans [11,12]. Our data collection included the patient impact of differences in the time required to administer the required tracers and to acquire scans. This demonstrated a significant difference in favour of PSMA PET/CT, even when the costs of attending hospital on separate days for acquisition of CT and bone scans were not considered.

The sensitivity analysis showed that the weighted cost per metastasis detection for ^{68}Ga-PSMA PET/CT was sensitive to the number of patients per elution. On the basis of the yields obtained per synthesis, between two and three patient doses could be regularly obtained. Clinical demand for PSMA PET/CT is likely to be high given the known incidence of prostate cancer, and our assumption of more than one patient dose per elution is therefore clinically applicable [11] and supports the dominance of PSMA PET/CT over CI.

The health resources identified are based on the proPSMA study and hence reflect the Australian clinical and institutional setting. Here, as in many European countries, gallium-68 generators can be used on site to produce the PSMA radioisotope [13,14]. By contrast, the USA has a centralised market for radiotracers, which may lead to differences in the use of resources and costs [15]. Our results were sensitive to the efficiency of the generator and associated costs, suggesting they may be generalisable to European countries with local on-site production that may reflect similar production efficiencies.

4.1. *Limitations*

Our costings are specific to the use of ^{68}Ga-PSMA-11 largely manufactured on site in hospital radiopharmacies. Further research is needed to confirm whether our results apply in other settings or indeed how the cost-effectiveness of PSMA PET/CT might alter in response to the radiopharmaceutical utilised [11]. Several other proprietary PSMA-targeting radiopharmaceuticals have been adopted clinically, including ^{18}F-DCFPyL and ^{18}F-PSMA-1007. These have potential for large-scale production and distribution, which could further reduce costs. The costs related to the proprietary nature of these ligands and production in compliance with good manufacturing practice, however, could alter this benefit. Although there are relatively minor differences, the largest volume of literature and experience is for ^{68}Ga-PSMA-11, and more data are required to confirm the performance of ^{18}F-labelled ligands. Advances with ^{68}Ga-PSMA-11 include kit-based production to increase efficiency [16] and cyclotron ^{68}Ga production that allows large-scale production analogous to ^{18}F [17]. Finally, it is important that subsequent research places the superiority of PSMA PET/

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CT for disease staging in context for the longer-term costs and outcomes of prostate cancer treatment.

5. Conclusions

PSMA PET/CT is dominant, with both lower direct comparative costs and greater accuracy when compared with CI for the detection of metastatic disease in men with high-risk prostate cancer. Combined with the other findings from proPSMA for patient management change, lower radiation exposure, and fewer equivocal findings, a compelling case can be made for adopting PSMA PET/CT.

Author contributions: Richard De Abreu Lourenco had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: de Feria Cardet, De Abreu Lourenco, Hofman, Frydenberg, Williams.
Acquisition of data: Hofman, de Feria Cardet, Segard, De Abreu Lourenco.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: de Feria Cardet, De Abreu Lourenco, Segard.
Obtaining funding: De Abreu Lourenco.
Administrative, technical, or material support: None.
Supervision: De Abreu Lourenco.
Other (validation of the model parameters): Hofman, Lawrentschuk, Williams.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2020.11.043.

References

[1] Perera M, Papa N, Roberts M, et al. Gallium-68 prostate-specific membrane antigen positron emission tomography in advanced prostate cancer—updated diagnostic utility, sensitivity, specificity, and distribution of prostate-specific membrane antigen-avid lesions: a systematic review and meta-analysis. Eur Urol 2020;77:403–17.
[2] Hofman MS, Lawrentschuk N, Francis RJ, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multi-centre study. Lancet 2020;395:1208–16.
[3] Segard T, Morandeau LM, Geelhoed EA, Francis RJ. ^{68}Ga-somatostatin analogue PET-CT: analysis of costs and benefits in a public hospital setting. J Med Imaging Radiat Oncol 2018;62:57–63.
[4] The Australian Department of Health. MBS Online. Medicare benefits schedule. www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/Home.
[5] Australian Bureau of Statistics. Employee earnings and hours, Australia. Reference period May 2018. www.abs.gov.au/statistics/labour/earnings-and-work-hours/employee-earnings-and-hours-australia/latest-release#:~:text=In%20May%202018%2C%20non%2Dmanagerial,cash%20earnings%20rate%20of%20%2439.10.
[6] Norum J, Nieder C. Treatments for metastatic prostate cancer (mPC): a review of costing evidence. Pharmacoeconomics 2017;35:1223–36.
[7] Scholte M, Barentsz JO, Sedelaar JPM, Gotthardt M, Grutters JPC, Rovers MM. Modelling study with an interactive model assessing the cost-effectiveness of ^{68}Ga prostate-specific membrane antigen positron emission tomography/computed tomography and nano magnetic resonance imaging for the detection of pelvic lymph node metastases in patients with primary prostate cancer. Eur Urol Focus 2020;6:967–74.
[8] Gordon LG, Elliott TM, Joshi A, Williams ED, Vela I. Exploratory cost-effectiveness analysis of ^{68}Gallium-PSMA PET/MRI-based imaging in patients with biochemical recurrence of prostate cancer. Clin Exp Metastasis 2020;37:305–12.
[9] Schwenck J, Olthof SC, Pfannenberg C, et al. Intention-to-treat analysis of ^{68}Ga-PSMA and ^{11}C-choline PET/CT versus CT for prostate cancer recurrence after surgery. J Nucl Med 2019;60:1359–65.
[10] Hofman MS, Murphy DG, Williams SG, et al. A prospective randomized multicentre study of the impact of gallium-68 prostate-specific membrane antigen (PSMA) PET/CT imaging for staging high-risk prostate cancer prior to curative-intent surgery or radiotherapy (proPSMA study): clinical trial protocol. BJU Int 2018;122:783–93.
[11] Afaq A, Alahmed S, Chen SH, et al. Impact of ^{68}Ga-prostate-specific membrane antigen PET/CT on prostate cancer management. J Nucl Med 2018;59:89–92.
[12] Evangelista L, Bonavina MG, Bombardieri E. Clinical results and economic considerations of ^{68}Ga-PSMA and radiolabeled choline in prostate cancer. Nucl Med Biol 2017;50:47–9.
[13] Prata MI. Gallium-68: a new trend in PET radiopharmacy. Curr Radiopharm 2012;5:142–9.
[14] Dash A, Chakravarty R. Radionuclide generators: the prospect of availing PET radiotracers to meet current clinical needs and future research demands. Am J Nucl Med Mol Imaging 2019;9:30–66.

[15] Lenzo NP, Meyrick D, Turner JH. Review of gallium-68 PSMA PET/CT imaging in the management of prostate cancer. Diagnostics 2018;8:16.

[16] Golan H, Esa M, Moshkoviz K, Feldhaim A, Hoch B, Shalom E. Enhancing capacity and synthesis of [^{68}Ga]68-Ga-PSMA-HBED-CC with the lyophilized ready-to-use kit for nuclear pharmacy applications. Nucl Med Commun 2020;41:986–90.

[17] Tieu W, Hollis CA, Kuan KKW, et al. Rapid and automated production of [^{68}Ga]gallium chloride and [^{68}Ga]Ga-DOTA-TATE on a medical cyclotron. Nucl Med Biol 2019;74-75:12–8.

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